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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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DEC 22 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Subject: EPA ID # 083501: Triethyelene glycol. Review of Phase IV response submissions in support of FIFRA 88

EPA Record Nos. S444604 & S444216
Caswell No. 888
PC Code: 083501
HED Project Nos. D193163 & D192934

From: Guruva B. Reddy, D.V.M., Ph. D. 12/15/93
Section 4
Toxicology Branch I
Health Effects Division (H7509C)

To: Barbara Briscoe/Emily Mitchell
Project Manager 81
Reregistration Division (H7508W)

Thru: Marion P. Copley, D.V.M., D.A.B.T. Marion Copley 12/15/93
Section Head
Section 4, Toxicology Branch I
Health Effects Division (H7509C)

1. **CONCLUSIONS:**

The published literature submitted for acute (oral, dermal, inhalation, eye and skin irritation and dermal sensitization), 90-day feeding, 21-day dermal, 90-day inhalation, chronic toxicity, oncogenicity, teratology, reproduction, mutagenicity and metabolism studies in support of triethylene glycol was reviewed and determined to be **ACCEPTABLE/WAIVED** as indicated below and to satisfy the requirements of their respective study guidelines. There are currently no data requirements pending for non-food use of triethylene glycol.

A copy of the DERs are attached.

cc: CCB (Chow; cover memo only)

2. **Action Requested:**

The CSMA Glycol Joint Venture representing the AMREP, Blue Coral, Inc., Claire Manufacturing Company, Cello Corporation/Grow Group, S.C. Johnson & Son, Inc., L & F Products, NCH Corporation, Sentry Chemical Company, Speer Products, Inc. and Waterbury Companies, Inc. submitted published literature for acute (oral, dermal, inhalation, eye and skin irritation and dermal sensitization), 90-day feeding, 21-day dermal, 90-day inhalation, chronic toxicity, oncogenicity, teratology, reproduction, mutagenicity and metabolism studies in support of triethylene glycol. This was in response to Phase IV of FIFRA 88 evaluation of their chemical. The information was reviewed and a copy of the DERs are attached.

3. **Data Requirements:**

Guideline #	Study Type	Required	Satisfied
81-1	Acute Oral Toxicity	Yes	Yes
81-2	Acute Dermal Toxicity	Yes	Waived
81-3	Acute Inhalation Toxicity	Yes	Yes
81-4	Primary Eye Irritation	Yes	Yes
81-5	Primary Dermal Irritation	Yes	Yes
81-6	Dermal Sensitization	Yes	Yes
82-1(a)	Subchronic Oral (rodent)	No	No
82-1(b)	Subchronic Oral (non-rodent)	Yes	Yes
82-2	21-day Dermal	Yes	Yes
82-4	90-day Inhalation (rodent)	Yes	Yes
83-1(b)	Chronic Toxicity (nonrodent)	Yes	Yes
83-2(a)	Oncogenicity (rodent)	Yes	Yes
83-3(a)	Teratology (rodent)	Yes	Yes
83-3	Teratology (non-rodent)	Yes	Yes
83-4	Reproduction (rodent)	Yes	Yes
84-2	Gene mutation (Ames)	Yes	Waived
84-2	Gene mutation (mammalian)	Yes	Waived
84-2	Structural chromosomal aberration	Yes	Waived
85-1	General Metabolism	Yes	Yes

4. **Studies reviewed:** DERs attached

Study/Classification	TB-I Comments
81-1. Acute Oral LD_{50} in rats MRID #: 428144-04 Published literature Acceptable; Tox. Cat. IV	The results are variable. The LD_{50}'s range from 15 - 22 g/kg.
81-2. Acute Dermal LD_{50} in rabbits Published literature MRID #: 428144-04 Tox. Cat. Not determined **Waived**	No appropriate reference was available to establish the toxicity category of the chemical. Data requirements waived based on the low-order of toxicity from various toxicity tests.
81-3. Acute Inhalation LD_{50} in rats Published literature #3147.24; December 20, 1988 MRID #: 428144-04 Acceptable; Tox. Cat. II	None of the studies determined the LC_{50} of the chemical. Monkeys and rats exposed by inhalation to about 1 ppm of triethylene glycol vapor for prolonged periods and humans exposed to air saturated with vapor (about 0.5 to 1 ppm) were without adverse physiological effects. The maximum tolerated level of triethylene glycol vapor in rats and mice was 800 mg/cubic mm or ≈ 0.8 mg/l. Preliminary results of intratracheal injection of 0.25 cc. undiluted triethylene glycol caused marked pulmonary irritation, acute edema and later fibrosis and abscess formation in rats; and was the basis for toxicity category.
81-4. Primary Eye Irritation in rabbits Published literature MRID #: 428144-04 Acceptable; Tox. Cat. III	No corneal opacity and no significant injury to mucous membranes after 24 hours. Other studies not adequate for regulatory purposes indicate negligible to appreciable irritation to the eye.
81-5. Primary Skin Irritation in rabbits Published literature MRID #: 428144-04 Acceptable; Tox. Cat. IV	Negligible to slight irritant to rabbit skin/humans; not irritant to human in 20% concentration in petrolatum.
81-6. Dermal Sensitization Published literature MRID #: 428144-04 Acceptable; Tox. Cat. N/A	Not a sensitizer in human volunteers when applied 20% in petrolatum.
82-1(b). 90-Day Feeding (nonrodent) Published literature MRID #: 428144-04 Minimum	Monkeys exposed continuously to saturated/slightly below saturated concentrations of triethylene glycol vapors or orally in egg nog of 50 (0.25 cc) to 100 (0.5 cc) times the glycol the animal could absorb by breathing air saturated with the glycol for 12 months, were without any adverse effects.
82-2. 21-Day Dermal in rabbits/rats Published literature MRID #: 428144-04 Minimum	Reported as the chemical is not absorbed through guinea-pig skin. Repeated application of 2 ml/rabbit for 6 weeks did not result in toxicity or macro- or microscopic skin changes.
82-4. 90-Day Inhalation - rat Published literature MRID #: 428144-04 Minimum	Monkeys and rats exposed by inhalation to about 1 ppm of triethylene glycol vapor for ≈ 12 months and humans exposed to air saturated with vapor (about 0.5 to 1 ppm) were without adverse physiological effects. The maximum tolerated level of triethylene glycol vapor in rats and mice was 800 mg/cubic mm or ≈ 0.8 mg/l.

Study/Classification	TB-I Comments
83-1(b). Chronic Toxicity - nonrodent Published literature MRID #: 428144-04 Minimum	Monkeys receiving triethylene glycol orally in egg nog of 50 (0.25 cc) to 100 (0.5 cc) times the glycol the animal could absorb by breathing air saturated with the glycol, for 12 months, were without any adverse effects.
83-2(a). Oncogenicity - rat Published literature MRID #: 428144-04 Minimum	Triethylene glycol administered in feed at levels of 0, 1, 2 or 4% (3 to 4 g/kg/day) to Osborn-Mendel rats for 2 years was not carcinogenic. In mice, intragastric administration of triethylene glycol resulted in one tumor, four papillomas and one planocellular cancer out of 80 mice tested.
83-3(a). Developmental toxicity - mouse Published literature MRID #: 428144-04 Minimum	Triethylene glycol administered orally at a dose of 11.27 grams/kg/day to timed pregnant CD-1 mice from gestation Days 7 through 14, resulted in maternal mortality (4%) and a significant reduction in pup weight gain; no other developmental toxicity was observed. Oral administration of triethylene glycol to pregnant rats, at a dose of 4.5 grams/kg/day, administered orally, were without teratogenic effects.
83-3(b). Developmental toxicity - rabbit Published literature MRID #: 428144-04 Minimum	Triethylene glycol administered subcutaneously at a dose of 2.25 g/kg/day during selected periods of pregnancy did not produce any teratogenic effects.
83-4. 2-Generation Reproduction - rat Published literature MRID #: 428144-04 Minimum	Rats exposed to an atmosphere saturated/nearly saturated with triethylene glycol ($\approx$ 1 ppm) continuously for 12 - 18 months, were without any adverse reproductive effects.
84-2(a). Mutagenicity (bacterial) - Ames Test Published literature MRID #: 428144-04 **Waived**	Based on the general metabolism of triethylene glycol in rats and rabbits, the sponsor perceives that the chemical is not expected to have an effect on DNA or any chromosomal activity. TB-I has no objection to the sponsor's assumption and recommend waiver of data requirements for this study.
84-2(a). Structural Chromosomal Aberration Published literature MRID #: 428144-04 **Waived**	Based on the general metabolism of triethylene glycol in rats and rabbits, the sponsor perceives that the chemical is not expected to have an effect on DNA or any chromosomal activity. TB-I has no objection to the sponsor's assumption and recommend waiver of data requirements for this study.
84-2(a). Mutagenicity - mammalian Study: Not submitted MRID #: N/A **Waived**	No data or information were presented for this study, however, based on the general metabolism of triethylene glycol in rats and rabbits and the justification provided by the sponsor for other mutagenicity studies, the TB-I recommends waiver of data requirements for this study.
85-1. General Metabolism Published literature MRID #: 428144-04 Minimum	In rats and rabbits, a considerable amount of the compound was excreted unchanged in the urine and glucuronide excretion was negligible. After oral doses, the rat and rabbit excreted triethylene glycol in both unchanged and oxidized forms. In rats, trace amounts (< 1%) of orally administered C^{14} triethylene glycol were excreted in respiratory carbon dioxide and detectable amounts in feces. The total elimination of radioactivity (urine, feces and CO_2) during the five day period following an oral dose of 22.5 mg was 91 - 98%. A major part of the radioactivity appeared in the urine.

5. **Data Gaps:**

There are no data gaps for non-food use of triethylene glycol. Published literature was used to satisfy the data requirements.

6. **Action Being Taken to Obtain Additional Information or Clarification:**

No actions are currently being taken. Published literature and long history of the use of triethylene glycol as air sanitizer without ill effects adequately satisfies the toxicity concerns for this chemical.

7. **Reference Dose (RfD):**

The chemical is for non-food use. No RfD is established for this chemical.

8. **Pending Regulatory Actions:**

The Toxicology Branch is unaware of any pending regulatory actions against this chemical.

9. **Toxicology Issues Pertinent to This Request:**

There are no toxicology issues to be addressed at this time.

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 11/14/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) Marion Copley 11/22/93

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity - rat (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 81-1

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. Fitzhugh, O, G. and Nelson, A. A.: Comparison of the chronic toxicity of triethylene glycol with that of diethylene glycol. J. Ind. Hyg. Toxicol., 28(2):40, 1946.

2. ____: Special Issue V. Monographs on Fragrance Raw Materials. Food and Cosmetic Toxicol., 17(suppl):913, 1979.

3. _____: Toxicological and Environmental Considerations. (source and date of publication is not given).

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: The results are variable. The LD_{50}'s are 16.8 cc/kg[1] (16.8 x 1.113 = 18.7 g/kg), 15 - 22 g/kg[2], 17 g/kg[2], 22 g/kg[3] and 22.06 g/kg[2].

CLASSIFICATION: Acceptable
TOX. CATEGORY: IV

The information presented for this acute oral toxicity in

rats satisfies the criteria set forth in Subdivision, F Series 81-1.

DISCUSSION: There is no raw data available. The above LD_{50} values are from monographs or review articles, which range from 15 - 22.06 g/kg. The values generally are in similar range and therefore considered acceptable.

Based on the above information, the compound is considered to be of low-order of toxicity and concluded as follows:

The information is Core-Acceptable
Toxicity Category IV

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DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity - rabbit/guinea pig (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 81-2

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORT CONSIDERED:

1. ____: Special Issue V. Monographs on Fragrance Raw Materials. Food and Cosmetic Toxicol., 17(suppl):913, 1979.

AUTHORS: None

REPORT ISSUED: N/A

CONCLUSIONS: Slightly irritating to rabbit skin in 24 hour occlusion test. No other information is available to determine dermal LD_{50}. Data requirements **waived** based on the low-order of toxicity of this chemical.

N A
CLASSIFICATION:
TOX. CATEGORY: Unknown

The information presented for this acute dermal toxicity study in rabbits/guinea pigs does not satisfy the criteria set forth in Subdivision, F Series 81-2; however the data satisfies the regulatory requirements (requirement is waived)

DISCUSSION: The referenced publication states that this chemical is not a good vehicle for dermal absorption in guinea pigs and is

slightly irritating to rabbit skin in a 24 hour occlusion test. Raw data is not available. Although the data from this reference is inadequate to establish the toxicity category of the chemical, **TB-I recommends waiver of data requirements for this chemical based on low-order of toxicity in other acute and chronic testing.**

Based on the information from various studies, this study is considered adequate to meet regulatory requirements.

The information is Supplementary
Toxic Category - Not determined

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DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation Toxicity - rat (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 81-3

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. ____: Special Issue V. Monographs on Fragrance Raw Materials. Food and Cosmetic Toxicol., 17(suppl):913, 1979.

2. _____: Toxicological and Environmental Considerations. (source and date of publication is not given).

3. Robertson, O. H., Loosli, C. G., Puck, T. T., Wise, H., Lemon, H. M. and Lester Jr., W.: Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. J. Pharm. Exp. Ther., 91:52, 1947.

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: None of the studies determined the LC_{50} of the chemical. Monkeys and rats exposed by inhalation to about 1 ppm of triethylene glycol vapor for prolonged periods and humans exposed to air saturated with vapor (about 0.5 to 1 ppm) were without adverse physiological effects. The maximum tolerated level of triethylene glycol vapor in rats and mice was

800 mg/cubic mm[1]. Preliminary results of intratracheal injection of 0.25 cc. undiluted triethylene glycol caused marked pulmonary irritation, acute edema and later fibrosis and abscess formation in rats.

CLASSIFICATION: Acceptable
TOX. CATEGORY: II

The information presented for this acute inhalation toxicity study in rats satisfies the criteria set forth in Subdivision, F Series 81-2.

METHODS: Standard guideline procedures were not used to generate aerosol vapors in this study[2]. Twenty-four males and 12 females, weighing 100 - 300 gm, were exposed to an atmosphere saturated with triethylene glycol 24 hours a day for ½ to 13 months. Six rats served as controls. Six rats/cage were maintained under above conditions and were bred on a limited basis. Saturated or supersaturated vapor of triethylene glycol was generated by placing a shallow dish of liquid on a hot plate heated to 100°C and blowing the vapor into the chamber using an electric fan. The chamber temperature of 77 - 82°F and relative humidity of 45% - 65% were maintained during the study. Rats were sacrificed at different intervals as noted in Table 1. A complete necropsy and histopathology were done. The number of rats in treated groups and controls increased to 60 and 14, respectively, due to new born during the study.

TABLE I

# KILLED	EXPOSURE (MONTHS)												TOTAL
	½	3	4	5	6	7	8	9	10	11	12	13	
TREATED	0	10	10	0	5	0	26	1	0	0	5	3	60
CONTROL	0	0	0	2	0	0	3	0	0	0	5	4	14

RESULTS: Preliminary results of intratracheal injection of 0.25 cc. undiluted triethylene glycol caused marked pulmonary irritation, acute edema and later fibrosis and abscess formation in rats. There were no deaths. All rats gained weight. No adverse reactions were observed.

DISCUSSION: This is not a classical study to establish the LC_{50} of the chemical. Basically, the study failed to demonstrate analytical and geometric concentration of the chemical in the chamber and Mass Median Aerodynamic Diameter (MMAD) of the aerosol particles. Except for the aforementioned, the study is much more extensive in demonstrating the effect of long term exposure to saturated or supersaturated concentration of the chemical. The chemical has a low-order of toxicity orally (LD_{50} 15 - 22 g/kg) and is not very well absorbed or not a good vehicle

for dermal absorption in guinea pigs; slightly irritating to rabbit skin in a 24 hour occlusion test. Although none of the studies met the guidelines, the studies cited below would facilitate establishing the toxicity category. From preliminary results of study 1 (800 mg/m^3 or ≈ 0.8 mg/l) it would appear that the chemical falls under Toxicity Category III, however, actual concentrations were not measured. The study referenced under 3 indicated that intratracheal injection of 0.25 cc. undiluted triethylene glycol resulting in marked pulmonary irritation, acute edema and later fibrosis and abscess formation in rats, the chemical is considered a severe irritant and would be classified as **Category II.** The TB-I considers the latter classification (Category II) as appropriate, unless the registrant wishes to conduct a new study using the current method.

Based on the above information, the data is considered adequate to determine inhalation toxicity, which is for labeling purposes only, and concluded as follows:

The information is Core-Acceptable
Toxicity Category - **II**

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Section IV, Tox. Branch I (H7509C)
Marion Copley 12/15/93

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation - rabbit (published literature)

TOX. CHEM. No.: 888

MRID No.: 428144-04

GUIDELINE #: 81-4

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORT:

1. Latven, A.R. and Molitor, H.: Comparison of the toxic and irritating properties of eight organic solvents. J. Pharm. Exp. Ther., **39**:89, 1939.

2. ____: Special Issue V. Monographs on Fragrance Raw Materials. Food and Cosmetic Toxicol., **17**(suppl):913, 1979.

3. _____: Toxicological and Environmental Considerations. (source and date of publication is not given).

4. Guillot, J.P., Martini, M.C., Giauffret, J.Y., Gonnet, J.F. and Guyot, J.Y.: Safety evaluation of some humectants and moisturizers used in cosmetic formulations. International J. of Cosmetic Sci., **4**:67, 1982.

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: There was no corneal opacity and no significant injury to mucous membranes after 24 hours[4]. Other studies not adequate for regulatory purposes indicate negligible[3], mild[1] or appreciable irritation[2].

CLASSIFICATION: Core-Acceptable
TOX. CATEGORY: III

The information presented for this primary eye irritation study in rabbits satisfy the criteria set forth in Subdivision, F Series 81-4.

METHODS:

In one study[1], 0.5 cc. of test compound was instilled into one eye of the rabbit and was held in place for one minute. Contralateral eye served as control. The eye(s) were evaluated for hyperemia, edema and corneal opacity at hourly intervals during first 4 hours after administration and at the end of 24 hours and daily for a week. The report indicated that the scores are the means of 90 experiments in rabbits; and the signs: +, ++, +++ indicate intensity of reaction.

In another study[4], 100% and 10% dilutions were tested. Dosages used and the number of rabbits in this study were not given, however, the procedures published in the Journal Official de le Republique Francaise was used in evaluating the irritation potential of triethylene glycol. The eyes were examined at 1, 24, 48, 72, 96 hours and 7 days after instillation. Fluorescein stain for corneal ulceration and ophthalmoscope and retinograph for qualitative evaluation of the eye were used. Eye irritation was scored on a scale of 0 to 110; a mean score of 15 or less were considered as non-irritating.

RESULTS: Among the studies listed above, no study indicated that triethylene glycol is a severe irritant. In one study[1] triethylene glycol was considered slightly more irritating than propylene glycol and was graded as a mild irritant. The results of well conducted study[4] did not show any irritation past 24 hours or corneal opacity; and the mean primary ocular irritation score was 11.33, which was considered normal. Several reviews reported the irritation potential of the triethylene glycol from failed to produce appreciable irritation[2] to negligible irritation[3].

DISCUSSION: Among the references furnished, only two references pertain to actual conduct of the studies. Other references were review articles. Generally, the data indicate that triethylene glycol is negligible to mild irritant, however, no raw data is available or its quality can be validated. Only reference 4 provides a reasonable description of methods which are (is) acceptable for testing cosmetics in Europe. Although the above information is marginal to satisfy data requirements for this study, toxicity information from various sources is generally consistent with the above findings and are acceptable.

Based on the above information, the data is considered adequate to determine primary eye irritation potential of triethylene glycol and concluded as follows:

The information is Core-Acceptable
Toxicity Category - III

C10715

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DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation - rabbit (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 81-5

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. Latven, A.R. and Molitor, H.: Comparison of the toxic and irritating properties of eight organic solvents. J. Pharm. Exp. Ther., **39**:89, 1939.

2. _____: Special Issue V. Monographs on Fragrance Raw Materials. Food and Cosmetic Toxicol., **17**(suppl):913, 1979.

3. _____: Toxicological and Environmental Considerations. (source and date of publication is not given).

4. Guillot, J.P., Martini, M.C., Giauffret, J.Y., Gonnet, J.F. and Guyot, J.Y.: Safety evaluation of some humectants and moisturizers used in cosmetic formulations. International J. of Cosmetic Sci., **4**:67, 1982.

AUTHORS: See above

CONCLUSIONS: The primary dermal irritation potential of triethylene glycol is negligible[1,3,4] to slightly irritating[2] to rabbit skin/humans. Other reports[2] indicated that triethylene glycol produced macerating action on prolonged contact and

produced no irritation in humans when applied 20% in petrolatum.

CLASSIFICATION: Core-Acceptable
TOX. CATEGORY: IV

The information presented for this primary dermal irritation study in rabbits satisfies the criteria set forth in Subdivision, F Series 81-5.

METHODS:

In one study[1], 2 sq. cm. gauze pads wetted with triethylene glycol was applied to shaven abdomen of rabbits and held in place with adhesive tape for 24 hours. The 24 hour evaluation indicated no irritation; however, there is no data to support the conclusions.

In another study[4], the chemical was used without dilution. The sponsor did not reference this publication in support of data requirement; in fact this is one of the most pertinent references. Neodermotest occlusive patches were held with absorbent gauze and adhesive bandage to the left and right flank of the rabbits and was evaluated according to the procedures published in the Journal Official de le Republique Francaise. The procedure did not provide any information on number of rabbits used and frequency of evaluations were done. Irritation was scored: non-irritant, < 0.5 and slightly irritant, 0.5 - 2.0.

RESULTS: The above studies indicated that the primary dermal irritation potential of triethylene glycol is negligible[1,3,4]. The mean dermal irritation score from study 4 was 0.08, which is negligible irritation. Other sources[2] reported that triethylene glycol produced a macerating action on prolonged contact, slight irritation on intact rabbit skin and no irritation in humans when applied 20% in petrolatum.

DISCUSSION: Among the references furnished, only two references pertain to actual conduct of the studies. Other references were review articles. Generally, the data indicate that triethylene glycol is a negligible to slight irritant to rabbit skin, however, no raw data is available or its quality can not be validated. Among the methods used, only reference 4 is credible and is the accepted methodology for testing cosmetics in Europe. Although the above information is marginal to satisfy data requirements for this study, toxicity information from various sources is generally consistent with the above findings and are acceptable.

Based on the above information, the data is considered adequate to determine primary dermal irritation potential of triethylene glycol and concluded as follows:

The information is Core-Acceptable
Toxicity Category - IV

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Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) 11/19/93

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 81-6

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. Guillot, J.P., Martini, M.C., Giauffret, J.Y., Gonnet, J.F. and Guyot, J.Y.: Safety evaluation of some humectants and moisturizers used in cosmetic formulations. International J. of Cosmetic Sci., **4**:67, 1982.

2. ____: Special Issue V. Monographs on Fragrance Raw Materials. Food and Cosmetic Toxicol., **17**(suppl):913, 1979.

AUTHORS: See above

CONCLUSIONS: Not a sensitizer in humans. A concentration of 20% in petrolatum was tested[2].

CLASSIFICATION: Core-Acceptable
TOX. CATEGORY: N/A

The information presented for this dermal sensitization study satisfies the criteria set forth in Subdivision, F Series 81-6.

DISCUSSION: Sponsor's cited reference[1] is inappropriate since propylene glycol instead of triethylene glycol was tested to

evaluate sensitization potential of the chemical. Reference 2 evaluated 20% triethylene glycol in petrolatum in human volunteers; and the chemical was not sensitizer. Although human testing is not guideline recommended, the eventual purpose is to test for human safety, therefore, the study is acceptable for the purpose.

Based on the above information, the data is considered adequate to determine dermal sensitization potential of triethylene glycol and concluded as follows:

The information is Core-Acceptable
Toxicity Category - N/A

C10715

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Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
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DATA EVALUATION REPORT

STUDY TYPE: 90-Day Feeding Study - nonrodent (published literature)

TOX. CHEM. No.: 888

MRID No.: 428144-04

PC CODE: 083501

GUIDELINE #: 82-1(b)

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. Robertson, O.H., Loosli, C.G., Puck, T.T., Wise, H., Lemon, H.M. and Lester, jr., W.: Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. J. Pharm. Exp. Ther., **91**:52, 1947.

2. Stenger, E.G., Aeppli, L., Peheim, E.u. and Roulet, F.C.: Zur Toxikologie des Triathylenglkol. Arzneimittel-Forsch. **18**:1536, 1968.

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: Monkeys exposed continuously to saturated/slightly below saturated concentrations of triethylene glycol vapors or orally in egg nog of 50 (0.25 cc) to 100 (0.5 cc) times the glycol the animal could absorb by breathing air saturated with the glycol for 12 months, were without any adverse effects.

CLASSIFICATION: Core-Minimum

The information presented for this 90-day feeding study in

monkeys (nonrodent) satisfies the criteria set forth in Subdivision, F Series 82-1(b).

DISCUSSION: There is no dog study which fits the criteria of subchronic studies, however, dogs given daily iv injections of 0.1 or 0.5 ml/kg for 4 weeks did not have toxicity or mortality, except for flattened epithelial cells in the urine and phlebitis at the site of injection[2]. Supplementary toxicity information from the chronic study (24-months, male, Osborn-Mendel rats), in which rats fed diets containing 1, 2 or 4% (3 to 4 g/kg/day) triethylene glycol show that the body weight gains, hematological and clinical chemistries were not effected; and was not tumorigenic (reference not included). In a 12 month study, monkeys exposed continuously to saturated/near saturated concentrations of triethylene glycol vapors or orally in egg nog of 50 (0.25 cc) to 100 (0.5 cc) times the glycol the animal could absorb by breathing air saturated with the glycol, did not adversely effect either the body physiological functions or the organ histopathology[1]. Although there is no guideline specific dog study is available, the information from monkey study is valuable since responses of this animal to changes in the environmental conditions approach much more nearly those of the humans than do the reaction of the common laboratory animals. Therefore, the information from this study is considered adequate to meet the data requirements for the nonrodent species and are acceptable.

Based on the above information, the data is considered adequate to for the dog study and concluded as follows:

The information is Core-Minimum

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 11/19/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) 11/19/93

DATA EVALUATION REPORT

STUDY TYPE: 21-Day Dermal Study - rabbit/rat (published literature)

TOX. CHEM. No.: 888

MRID No.: 428144-04

PC CODE: 083501

GUIDELINE #: 82-2

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. ____: Special Issue V. Monographs on Fragrance Raw Materials. Food and Cosmetic Toxicol., 17(suppl):913, 1979.

2. Guillot, J.P., Martini, M.C., Giauffret, J.Y., Gonnet, J.F. and Guyot, J.Y.: Safety evaluation of some humectants and moisturizers used in cosmetic formulations. International J. of Cosmetic Sci., 4:67, 1982.

AUTHORS: None

REPORT ISSUED: N/A

CONCLUSIONS: Reported as: the chemical is not absorbed through guinea-pig skin[1]. Repeated application of 2 ml/rabbit for 6 weeks did not result in toxicity or macro- or microscopic skin changes[2].

CLASSIFICATION: Core-Minimum

The information presented for this 21 Day Dermal Study in rabbits satisfies the criteria set forth in Subdivision, F Series 82-2.

DISCUSSION: The sponsor referenced publication is inappropriate to establish the safety of triethylene glycol, which stated that the chemical is not a good vehicle for dermal absorption in guinea pigs[1]. The study cited under reference 2 is appropriate for this guideline series. In this study, repeated dermal application of 2 ml/rabbit of the chemical for 6 weeks did not result in any toxicity or macro- or microscopic dermal changes. This study is considered adequate to satisfy data requirements for 21 day dermal study in rabbits.

Based on the above information, the study is classified as Core-**Minimum**.

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 11/19/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) Marion Copley 11/22/93

DATA EVALUATION REPORT

STUDY TYPE: 90-Day Inhalation Study - rat (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 82-4

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. Robertson, O. H., Loosli, C. G., Puck, T. T., Wise, H., Lemon, H. M. and Lester Jr., W.: Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. J. Pharm. Exp. Ther., **91**:52, 1947.

2. Goldstein, I., Dumitro, E., David, V. and Melinte, L.: Toxicity of glycol derivatives. Igiena, **19**: 209, 1970.

3. Harris, T.M. and Stokes, J.: Summary of three year study of the clinical application of disinfection of air by glycol vapor. Am. J. Med. Sci., **209**:152, 1945

4. Jennings, B.H., Biggs, E. and Olson, F.C.W.: Heat. Pip. Air Condit., **16**:538, 1944.

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: Monkeys and rats[1] exposed by inhalation to about 1 ppm of triethylene glycol vapor for ≈ 12 months and humans[3,4] exposed to air saturated with vapor (about 0.5 to 1 ppm) were without adverse physiological effects. The maximum tolerated

level of triethylene glycol vapor in rats and mice was 800 mg/cubic mm[2].

CLASSIFICATION: Core - Minimum

The information presented for the 90-day inhalation study in rats satisfies the criteria set forth in Subdivision, F Series 82-4.

METHODS: Standard guideline procedures were not followed to generate aerosol vapors in this study[3]. Twenty-four males and 12 females, weighing 100 - 300 gm, were exposed to an atmosphere saturated with triethylene glycol 24 hours a day for ½ to 13 months. Six rats served as controls. Six rats/cage were maintained under above conditions and were bred on a limited basis. Saturated or supersaturated vapor of triethylene glycol was generated by placing a shallow dish of liquid on a hot plate heated to 100°C and blowing the vapor into the chamber using an electric fan. The chamber temperature of 77 - 82°F and relative humidity of 45% - 65% were maintained during the study. Rats were sacrificed at different intervals as noted in Table 1. A complete necropsy and histopathology were done. The number of rats in treated groups and controls increased to 60 and 14, respectively, due to new born during the study.

TABLE I

# KILLED	EXPOSURE (MONTHS)												TOTAL
	½	3	4	5	6	7	8	9	10	11	12	13	
TREATED	0	10	10	0	5	0	26	1	0	0	5	3	60
CONTROL	0	0	0	2	0	0	3	0	0	0	5	4	14

RESULTS: There were no deaths. All animals gained weight. No adverse reactions were observed.

DISCUSSION: In this study, rats and monkeys exposed to saturated or supersaturated concentration of the chemical for prolonged periods did not show any treatment-related adverse reactions or histopathological changes suggestive of toxicity. Although the study was not conducted as per the guidelines, the conditions of the study (length and frequency of exposure was 3 times the recommended) were harsher and are considered adequate to elicit toxic potential of the chemical. Data from the acute studies indicated that the chemical has a low-order of toxicity orally (LD_{50} 15 - 22 g/kg) and is not very well absorbed or not a good vehicle for dermal absorption in guinea pigs; slightly irritating to rabbit skin in a 24 hour occlusion test. Further, human volunteers exposed to air saturated with triethylene glycol vapor (about 0.5 to 1 ppm) were without adverse physiological effects[3,4]. Based on the above information, the study is

considered adequate to fulfill the regulatory requirements and is classified as Core-**Minimum**.

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 11/17/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) 4/22/93

DATA EVALUATION REPORT

STUDY TYPE: Chronic Toxicity - nonrodent (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 83-1(b)

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. Robertson, O.H., Loosli, C.G., Puck, T.T., Wise, H., Lemon, H.M. and Lester, jr., W.: Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. J. Pharm. Exp. Ther., **91**:52, 1947.

2. Stenger, E.G., Aeppli, L., Peheim, E.u. and Roulet, F.C.: Zur Toxikologie des Triathylenglkol. Arzneimittel-Forsch. **18**:1536, 1968.

3. Fitzhugh, O, G. and Nelson, A. A.: Comparison of the chronic toxicity of triethylene glycol with that of diethylene glycol. J. Ind. Hyg. Toxicol., 28(2):40, 1946.

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: Monkeys receiving triethylene glycol orally in egg nog of 50 (0.25 cc) to 100 (0.5 cc) times the glycol the animal could absorb by breathing air saturated with the glycol, for 12 months, were without any adverse effects.

CLASSIFICATION: Core-Minimum

The information presented for this chronic toxicity study in monkeys (nonrodent) satisfies the criteria set forth in Subdivision, F Series 82-1(b).

DISCUSSION: There is no dog study which could fit the criteria of chronic studies, however, dogs given daily 0.1 or 0.5 ml/kg iv injections of triethylene glycol for 4 weeks did not show toxicity or mortality, except for flattened epithelial cells in the urine and phlebitis at the site of injection[2]. Supplementary toxicity information from the chronic study (24-months, male, Osborn-Mendel rats), in which rats fed diets containing 1, 2 or 4% (3 to 4 g/kg/day) triethylene glycol show that the body weight gains, hematological and clinical chemistries were not effected; and was not tumorigenic[3]. In a 12 month study, monkeys receiving triethylene glycol orally in egg nog of 50 (0.25 cc) to 100 (0.5 cc) times the glycol the animal could absorb by breathing air saturated with the glycol, did not adversely effect either the body physiological functions or the organ histopathology[1]. Although there is no guideline specific dog study is available, the information from monkey study is valuable since responses of this animal to chemical exposure approaches much more nearly those of the humans than do the reaction of the common laboratory animals. Therefore, the information from this study is considered adequate to meet the regulatory requirements for the nonrodent species and are acceptable.

Based on the above information, the data is considered adequate to for the dog study and concluded as follows:

The information is Core-Minimum

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 11/19/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) 11/19/93

DATA EVALUATION REPORT

STUDY TYPE: Oncogenicity - rat (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 83-2(a)

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. Fitzhugh, O, G. and Nelson, A. A.: Comparison of the chronic toxicity of triethylene glycol with that of diethylene glycol. J. Ind. Hyg. Toxicol., **28**(2):40, 1946.

2. ____: Special Issue V. Monographs on Fragrance Raw Materials. Food and Cosmetic Toxicol., **17**(suppl):913, 1979.

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: Triethylene glycol administered in feed at levels of 0, 1, 2 or 4% (3 to 4 g/kg/day) to Osborn-Mendel rats for 2 years was not carcinogenic[1]. In mice, intragastric administration of triethylene glycol resulted in one tumor, four papillomas and one planocellular cancer out of 80 mice tested[2].

CLASSIFICATION: Core-Minimum

The information presented for this oncogenicity study in rats satisfies the criteria set forth in Subdivision, F Series 83-2(a).

DISCUSSION: Toxicity information from the chronic study (24-months, male, Osborn-Mendel rats), in which rats fed diets containing 1, 2 or 4% (3 to 4 g/kg/day) triethylene glycol, show that the body weight gains, hematological and clinical chemistries were not effected; and was not tumorigenic[1]. In the mouse study, tumors (1/80 tumor, 4/80 papillomas and 1/80 planocellular cancer) were noticed, but the levels tested were not known[2]. Levels tested in Osborn-Mendel rats are well above the upper limit of 1 gram/kg for testing pesticides (Theodore M. Farber, presented at S.O.T. Symposium on MTD., Feb. 26, 1987). There is no reason to believe that tumors would be present in females at doses < 1 g/kg. Therefore, the information from this study is considered adequate to meet the regulatory requirements for the rodent species and are acceptable.

Based on the above information, the data is considered adequate to for the oncogenicity study in rats and concluded as follows:

The information is Core-**Minimum**

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 11/19/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) Marion Copley 4/22/93

DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity - mouse (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 83-3(a)

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. Schuler, R.L., Hardin, B.D., Niemeier, R.W., Booth, G., Hazelden, K., Piccirillo, V. and Smith, K.: Results of testing fifteen glycol ethers in a short-term <u>in vivo</u> reproductive assay. Environmental Health perspectives, **57**:141, 1984.

2. Hardin, B.D., Schuler, R.L., Burg, J.R., Booth, G.M., Hazelden, K.P., MacKenzie, K.M., Piccirillo, V.J. and Smith, K.N.: Evaluation of 60 chemicals in a preliminary developmental toxicity test. Teratogenesis, Carcinogenesis, and Mutagenesis, **7**:29, 1987.

3. Rowe, V.K. and Wolf, M.A.: Glycols. Triethylene Glycol. (referenced but source was not provided).

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: Triethylene glycol administered orally at a dose of 11.27 grams/kg/day to timed pregnant CD-1 mice from gestation Days 7 through 14, resulted in maternal mortality (4%) and a

significant reduction in pup weight gain; no other developmental toxicity was observed[1,2]. Oral administration of triethylene glycol to pregnant rats, at a dose of 4.5 grams/kg/day, administered orally, were without teratogenic effects.

CLASSIFICATION: Core-**Minimum**

The information present for this developmental toxicity study in mouse satisfies the criteria set forth in Subdivision, F Series 83-3(a).

DISCUSSION: References 1 and 2 are based on same data; the study is well conducted. Reference 3 is a chapter on glycols and does not give any details of the study or the source of the reference. The information presented is considered adequate for the regulatory purpose and concluded as follows:

The information is Core-**Minimum**

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 11/19/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) Marion Copley 11/22/93

DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity - rabbit (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 83-3(b)

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORT:

1. Rowe, V.K. and Wolf, M.A.: Glycols. Triethylene Glycol. (referenced but source was not provided).

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: Triethylene glycol administered subcutaneously at a dose of 2.25 g/kg/day during selected periods of pregnancy did not produce any teratogenic effects.

CLASSIFICATION: Core-Minimum

The information presented for this developmental toxicity study in rabbits satisfies the criteria set forth in Subdivision. F Series 83-3(b).

DISCUSSION: This reference is part of a chapter on glycols, which lacks details of the study or the source of the reference. Further the route of administration is not appropriate for testing this chemical. Since the chemical was not teratogenic to rats at 4.5 g/kg/day, the information on rabbit developmental NOEL of 2.25 g/kg/day appear reasonable and considered adequate

to meet the regulatory requirements.

The information is Core-**Minimum**

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Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 11/19/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) 11/22/93

DATA EVALUATION REPORT

STUDY TYPE: Two-Generation Reproduction Study - rat (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 83-4

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. Schuler, R.L., Hardin, B.D., Niemeier, R.W., Booth, G., Hazelden, K., Piccirillo, V. and Smith, K.: Results of testing fifteen glycol ethers in a short-term in vivo reproductive assay. Environmental Health perspectives, **57**:141, 1984.

2. Hardin, B.D., Schuler, R.L., Burg, J.R., Booth, G.M., Hazelden, K.P., MacKenzie, K.M., Piccirillo, V.J. and Smith, K.N.: Evaluation of 60 chemicals in a preliminary developmental toxicity test. Teratogenesis, Carcinogenesis, and Mutagenesis, 7:29, 1987.

3. Robertson, O. H., Loosli, C. G., Puck, T. T., Wise, H., Lemon, H. M. and Lester Jr., W.: Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. J. Pharm. Exp. Ther., 91:52, 1947.

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: The only reference which has some relevance to the study type is the reference 3, which states that rats exposed to an atmosphere saturated/nearly saturated with triethylene glycol (≈ 1 ppm) continuously for 12 - 18 months, were without any adverse reproductive effects[3]. Other references cited in support of this study are inappropriate.

CLASSIFICATION: Core-Minimum

The information presented for this two-generation reproduction study in rats satisfies the criteria set forth in Subdivision, F Series 83-4.

DISCUSSION: References 1 and 2 are based on the same data. The study is well conducted, however not pertinent to the study type. In this mouse study, oral administration of triethylene glycol at a dose level of 11.27 grams/kg/day, during the gestation Days 7 through 14, resulted in 4% maternal mortality and a significant reduction in weight gain of pups. The aforementioned study would appropriately fulfill the regulatory requirements for developmental toxicity data but not the reproduction study.

Reference 3 is the only study which has some relevance to this guideline series. The data indicates that rats exposed to an atmosphere saturated/nearly saturated (≈ 1 ppm) with triethylene glycol for prolonged periods (12 - 18 months) were without any adverse clinical or reproductive effects. Although none of the referenced studies met the guideline requirements, the data from the above studies and listing of the chemical under the Food Additive Regulations (21 CFR; Food and Drug Administration) and exemption form requirement to establish tolerances (40 CFR §180.1001), would support the finding that the chemical was not associated with any reproductive effects. Therefore, the information is considered adequate to fulfill the regulatory requirements for two-generation reproduction study in rats.

The information is Core-**Minimum**

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 11/1/93 12/04/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) Marion Copley 11/22/93

DATA EVALUATION REPORT

STUDY TYPE: Gene Mutation - Ames (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 84-2(a)

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. ____: Special Issue V. Monographs on Fragrance Raw Materials. Food and Cosmetic Toxicol., **17**(suppl):913, 1979.

2. McKennis, Jr., H., Turner, R.A., Turnbull, L.B., Bowman, E.R., Muelder, W.W., Neidhardt, M.P., Hake, C.L. Henderson, R., Nadaeu, H.G. and Spencer, S.: The Excretion and Metabolism of Triethylene Glycol. Toxic. Appl. Pharmac., **91**:52, 1962.

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: Based on the general metabolism of triethylene glycol in rats and rabbits, the sponsor perceives that the chemical is not expected to have an effect on DNA or any chromosomal activity. TB-I has no objection to the sponsor's assumption and recommend waiver of data requirements for this study.

CLASSIFICATION: Data requirements waived

DISCUSSION: Direct evidence with regard to non-mutagenicity of the compound was not presented. The sponsor is perceiving

that the chemical is not expected to have an effect on DNA or any chromosomal entity, based on metabolism data which indicate that about 98% of the administered triethylene glycol was eliminated in urine, feces and respirable carbon dioxide [very low or negligible amounts (< 1%)]. Most of the chemical was recovered in urine unchanged. Further the chemical was not found to be carcinogenic in rat and mouse studies. Based on the above information and low order of toxicity from laboratory animals and human exposure, it is logical to support the sponsor's contention and recommend **waiver** of data requirements for this study.

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 11/19/93 12/01/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) Marion Copley 4/22/94

DATA EVALUATION REPORT

STUDY TYPE: Structural Chromosomal Aberration (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 84-2(b)

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. ____: Special Issue V. Monographs on Fragrance Raw Materials. Food and Cosmetic Toxicol., **17**(suppl):913, 1979.

2. McKennis, Jr., H., Turner, R.A., Turnbull, L.B., Bowman, E.R., Muelder, W.W., Neidhardt, M.P., Hake, C.L. Henderson, R., Nadaeu, H.G. and Spencer, S.: The Excretion and Metabolism of Triethylene Glycol. Toxic. Appl. Pharmac., **91**:52, 1962.

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: Based on the general metabolism of triethylene glycol in rats and rabbits, the sponsor perceives that the chemical is not expected to have an effect on DNA or any chromosomal activity. TB-I has no objection to the sponsor's assumption and recommend waiver of data requirements for this study.

CLASSIFICATION: Data requirements waived

DISCUSSION: Direct evidence with regard to lack of chromosomal

activity of the compound was not presented. The sponsor is perceiving that the chemical is not expected to have an effect on DNA or any chromosomal entity, based on metabolism data which indicate that about 98% of the administered triethylene glycol was eliminated in urine, feces and respirable carbon dioxide [very low or negligible amounts (< 1%)]. Most of the chemical was recovered in urine unchanged. Further the chemical was not found to be carcinogenic in rat and mouse studies. Based on the above information and low order of toxicity from laboratory animals and human exposure, it is logical to support the sponsor's contention and recommend **waiver** of data requirements for this study.

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 11/1-1/93 12/01/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) Marion Copley

DATA EVALUATION REPORT

STUDY TYPE: Gene Mutation - Mammalian

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: None

GUIDELINE #: 84-2(a)

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: None submitted

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. ____: Special Issue V. Monographs on Fragrance Raw Materials. Food and Cosmetic Toxicol., **17**(suppl):913, 1979.

2. McKennis, Jr., H., Turner, R.A., Turnbull, L.B., Bowman, E.R., Muelder, W.W., Neidhardt, M.P., Hake, C.L. Henderson, R., Nadaeu, H.G. and Spencer, S.: The Excretion and Metabolism of Triethylene Glycol. Toxic. Appl. Pharmac., **91**:52, 1962.

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: No data or information were presented for this study, however, based on the general metabolism of triethylene glycol in rats and rabbits and the justification provided by the sponsor for other mutagenicity studies, the TB-I recommends **waiver** of data requirements for this study.

CLASSIFICATION: Data requirements waived

DISCUSSION: Neither data nor information with regard to non-mutagenicity of the compound for this study were presented.

However, the sponsor concluded in support of other mutagenicity studies that the chemical is not expected to have an effect on DNA or any chromosomal entity. This was based on metabolism data which indicated that about 98% of the administered triethylene glycol was eliminated in urine, feces and respirable carbon dioxide [very low or negligible amounts (< 1%)]. Most of the chemical was recovered in urine unchanged. Further the chemical was not found to be carcinogenic in rat and mouse studies. Based on the above information and low order of toxicity from laboratory animals and human exposure, it is logical to support the sponsor's contention and recommend **waiver** of data requirements for this study.

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 11/19/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) 11/22/93

DATA EVALUATION REPORT

STUDY TYPE: General Metabolism (published literature)

TOX. CHEM. No.: 888

PC CODE: 083501

MRID No.: 428144-04

GUIDELINE #: 85-1

TEST MATERIAL: Triethylene glycol

SYNONYMS: N/A

STUDY NUMBERS: Published literature

SPONSOR: CSMA Glycols Joint Venture Member Companies

TESTING FACILITY: N/A

TITLE OF REPORTS CONSIDERED:

1. ____: Special Issue V. Monographs on Fragrance Raw Materials. Food and Cosmetic Toxicol., **17**(suppl):913, 1979.

2. McKennis, Jr., H., Turner, R.A., Turnbull, L.B., Bowman, E.R., Muelder, W.W., Neidhardt, M.P., Hake, C.L. Henderson, R., Nadaeu, H.G. and Spencer, S.: The Excretion and Metabolism of Triethylene Glycol. Toxic. Appl. Pharmac., **91**:52, 1962.

AUTHORS: See above

REPORT ISSUED: N/A

CONCLUSIONS: In rats and rabbits, a considerable amount of the compound was excreted unchanged in the urine and glucuronide excretion was negligible[1]. After oral doses, the rat and rabbit excreted triethylene glycol in both unchanged and oxidized forms[2]. In rats, trace amounts (< 1%) of orally administered C^{14} triethylene glycol were excreted in respiratory carbon dioxide and detectable amounts in feces. The total elimination of radioactivity (urine, feces and CO_2) during the five day period following an oral dose of 22.5 mg was 91 - 98%. A major part of the radioactivity appeared in the urine.

CLASSIFICATION: Core-**Minimum**

The information presented for this general metabolism study in rats satisfies the criteria set forth in Subdivision, F Series 85-1.

DISCUSSION: References 1 is a monograph on triethylene glycol which summarized the literature and quoted that the compound was eliminated unchanged in the urine. A well conducted study which used the C^{14} triethylene glycol is cited under reference 2. The data indicated that ≈ 1% of the administered radioactivity appeared as respirable carbon dioxide. During the 5 days following oral administration of 22.5 mg of labeled compound, 91 - 98% of radioactivity appeared in the urine, feces and CO_2. A major portion of the radioactivity was present in the urine.

The information is Core-**Minimum**

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Chemical:	**Triethylene glycol**
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